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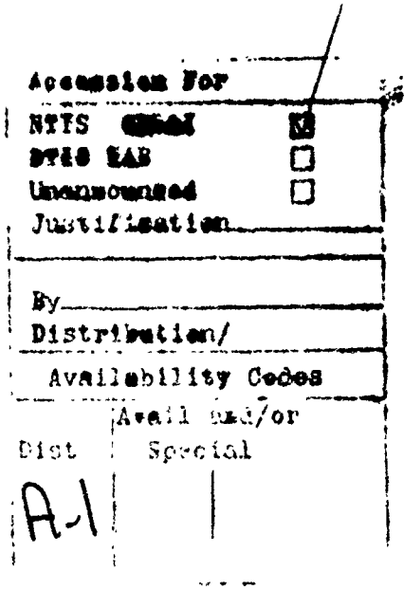

The topochemical basis for morphiceptin and dermorphin bioactivity

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Introduction

Morphiceptin (Tyr^1-Pro^2-Phe^3-Pro^4-NH_2) and dermorphin (Tyr^1-D-Ala^2-Phe^3-Gly^4-Tyr^5-Pro^6-Ser^7-NH_2) are highly μ-receptor selective peptide opioids. Since the biologically important Tyr^1 and Phe^3 are joined by a single amino acid, the second residue plays a significant role to orient these residues in the correct array necessary for bioactivity. These two classes of opioids exhibit opposite chiral requirements at residue 2. Incorporation of L-amino acids at position 2 of dermorphin results in a remarkable reduction in bioactivity. Morphiceptin requires an L-chirality for Pro^2. Because of Pro at position 2, morphiceptin exhibits cis and trans isomers about the Tyr^1-Pro^2 amide bond (30:70) [1]. We incorporated 2-aminocyclopentanecarboxylic acid (2-Ac^{5}c) for Pro^2. Among the four stereoisomers, only the morphiceptin analog containing *cis*-(1S,2R)-2-Ac^{5}c shows bioactivity. Although the 2-Ac^{5}c analogs adopt a trans amide bond about Tyr-2-Ac^{5}c, the bioactive analog Tyr-(1S,2R)-2-Ac^{5}c-Phe-Pro-NH_2 is topologically similar to morphiceptin with the Tyr-Pro amide bond in a cis configuration [2].

To extend the work on conformation-bioactivity relationships for morphiceptin and dermorphin, we synthesized tetrapeptides incorporating (L and D)-(NMe)Ala and Ala in place of Pro^2 of the active Tyr-Pro-Phe-D-Pro-NH_2. Accessible at conformational space for the second residues of Tyr-(L and D)-X-Phe-D-Pro-NH_2 [X = Ala, Pro, and L and D(NMe)Ala] and conformational preferences of various morphiceptin and dermorphin analogs, studied by ^{1}H NMR spectroscopy and molecular modeling, allowed us to develop specific topologies necessary for bioactivity of peptide opioids containing Phe at the third position.

Results and Discussion

The (NMe)Ala^2 analog is potent, displaying the similar activity profile as the Pro^2 analog. The analog Tyr-Ala-Phe-D-Pro-NH_2 is inactive. Upon N-methylation of Ala, Tyr-(NMe)Ala-Phe-D-Pro-NH_2 exhibits cis and trans forms about the amide bonds between residues 1 and 2 (29:71) similar to Tyr-Pro-Phe-D-Pro-NH_2 (28:72). The D-(NMe)Ala^2 analog is also biologically active, displaying the same potency as the dermorphin analog Tyr-D-Ala-Phe-D-Pro-NH_2. The ratio

Table 1 *Selected torsion angles (deg) for bioactive conformations of the morphiceptin and dermorphin analogs*

Analog	Tyr[1]			Second residue			(L or D)-Phe[3]	
	ψ	χ_1	ω	ϕ	ψ	ω	ϕ	χ_1
Tyr-Pro-Phe-D-Pro-NH_2	130	180	0	-75	130	180	-110	180
Tyr-Pro-D-Phe-D-Pro-NH_2	130	180	0	-75	-40	180	100	180
Tyr-(NMe)Ala-Phe-D-Pro-NH_2	130	180	0	-85	120	180	-90	80
Tyr-D-(NMe)Ala-Phe-D-Pro-NH_2	130	180	180	130	90	180	-140	180

of 19 : 81 was observed for cis and trans configurational isomers about the amide bond between residues 1 and 2 in Tyr-D-(NMe)Ala-Phe-D-Pro-NH_2.

Accessible conformational space for the second residues of Tyr-(L and D)-X-Phe-D-Pro-NH_2 [X = Ala, Pro and (NMe)Ala] based on ^1H NMR and molecular modeling shows that the (NMe)Ala[2] analog belongs to the morphiceptin opioids, whose high μ-receptor activities are attributed to conformations with the Tyr-X amide bond in a cis configuration. On the other hand, the μ-receptor activity of the D-(NMe)Ala[2] analog is attributed to conformations, in which the Tyr-D-(NMe)Ala amide bond adopts a trans configuration, and therefore belongs to the dermorphin opioids.

Structures of Tyr-(NMe)Ala-Phe-D-Pro-NH_2 and Tyr-D-(NMe)Ala-Phe-D-Pro-NH_2, considered to be closely related to bioactive forms at the μ-receptors, are shown in Figs. 1a and 1b, respectively. The relative spatial arrangements of the functional groups, i.e., the amine and phenolic groups of Tyr[1] and the aromatic ring of Phe[3], are almost the same in both the structures. However, the conformations of the second residues in these structures are different from each other (Table 1). It is worthwhile mentioning that the bioactive conformations of the morphiceptin and dermorphin analogs estimated in this investigation are

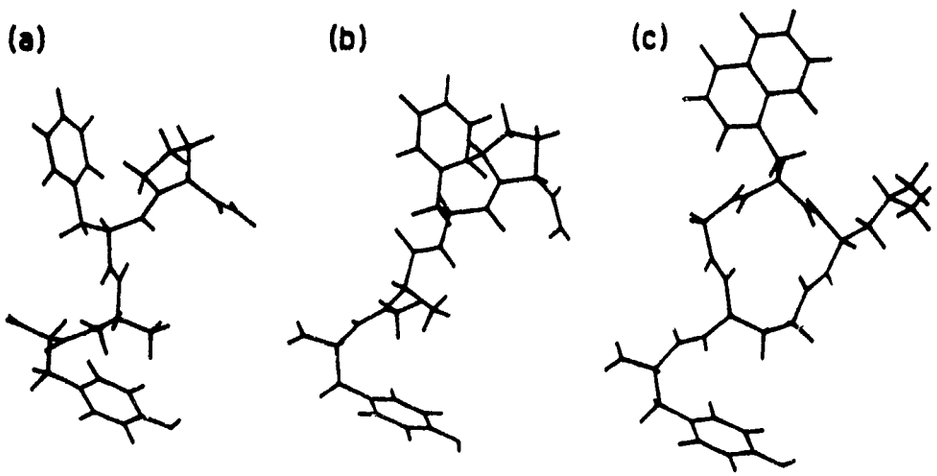

Fig. 1. Preferred conformations of (a) Tyr-(NMe)Ala-Phe-D-Pro-NH_2, (b) Tyr-D-(NMe)Ala-Phe-D-Pro-NH_2, and (c) Tyr-c[D-A$_2$bu-Gly-βNal(1)-D-Leu^9] at the μ-receptors.

topologically similar to the μ-receptor active conformation of the enkephalin analog with a β-naphthylalanine at position 4 (Fig. 1c) [3]. Topological similarity of the preferred conformations of the morphiceptin, dermorphin, and enkephalin analogs at the μ-receptors indicates that these three classes of peptide opioids may interact with the same μ-receptors.

References

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